

MEDICAL STAFF CONFERENCE

The Clinical Spectrum of Sjögren's Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* Mikulicz first described the pathological changes in the salivary and lacrimal glands and the associated clinical manifestations. In the following years there were other contributions relating to this interesting syndrome. These contributions were culminated in the excellent clinical work of the Swedish ophthalmologist, Henrich Sjögren, in the 1930's. It is part of the injustice of medical history that this syndrome has become known as Sjögren's syndrome, and Mikulicz's syndrome has been somewhat submerged. The Medical Staff Conference today will be devoted to a consideration of this interesting disorder. The case history will be given by Dr. Watts.

DR. WATTS:† The patient is a 68-year-old caucasian woman who presented with the chief complaint of dry eyes and mouth. Her present illness began two years before admission when pruritus developed in association with increasing dryness and redness of the skin. The dryness of mouth caused some interference with speech and swallowing, and the patient noted a grainy sensation and dryness of her eyes. Dryness and pruritus of the vaginal mucosa were also prominent complaints. The patient also fatigued easily and experienced an increase in dental caries over the same period of time. The patient's past medical

history was unremarkable except for a possible allergic sensitivity to penicillin. On physical examination the patient's blood pressure was 160/90 mm of mercury, pulse 100 beats per minute, and respirations 18 per minute. The skin was dry and scaly, the parotid glands slightly enlarged but not tender. The Schirmer test showed 10 mm of bilateral wetting. No abnormalities were noted on examination of the heart, lungs and abdomen, and there were no pathologic changes in the joints. The erythrocyte sedimentation rate was 36 mm in one hour. Leukocytes numbered 3,000 per cu mm with 52 percent polymorpholeukocytes. The blood sugar was normal, and the serum uric acid was 8.9 mg per 100 ml. Serum protein electrophoresis showed a slightly elevated gamma globulin fraction, and there was a positive antinuclear antibody with a speckled pattern. The rheumatoid factor was positive at a 1 to 3,200 titer. An x-ray film of the chest and electrocardiogram were within normal limits.

During the stay in hospital, salivary scintigraphy with 99m technetium showed a decreased accumulation in the parotid glands. There was only transient uptake in the submandibular glands, and there was no accumulation of the label in the mouth during the course of the study. The findings were interpreted as very abnormal. A sialogram was normal on the right side and abnormal on the left. A lip biopsy revealed in-

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creased infiltration of plasma cells and lymphocytes, as well as hyperplasia of the epithelial cells of the salivary ducts. Thickening of the walls of the salivary ducts and a moderate increase of connective tissue throughout the stroma were also observed. These findings were consistent with the diagnosis of Sjögren's syndrome.

DR. SMITH: We are pleased to have Dr. Martin Shearn to discuss this case. Dr. Shearn has had a long time interest in this syndrome and has recently published a superb monograph on this topic.

DR. MARTIN A. SHEARN: * Thank you, Dr. Smith. Perhaps we can define Sjögren's syndrome as a chronic inflammatory disorder, characterized by dryness of the mouth, eyes, and other mucous membranes, and frequently associated with a rheumatic disease. Today's patient illustrates a number of the clinical characteristics of Sjögren's syndrome. She presented with dryness of the eyes, mouth, and vagina. She had the typical serological reactivity so often seen in Sjögren's syndrome, manifested by hypergammaglobulinemia and positive reactions to tests for antinuclear antibody and rheumatoid factor. Confirmatory evidence for the diagnosis is offered by the characteristic histopathology in her minor salivary glands.

Ocular Tests

Although Sjögren's syndrome is a systemic disorder, the diagnosis may most often be established by directing attention to the eyes and salivary glands. The anterior surface of the normal eye is protected by a tear film made up largely of lacrimal secretions. In Sjögren's syndrome there is atrophy of the secretory epithelium of both the major and the minor lacrimal glands, leading to desiccation of the cornea and conjunctiva (keratoconjunctivitis sicca). In advanced cases, the cornea may undergo severe damage; in such instances, epithelial strands are seen hanging down from the corneal surface (keratitis filiformis), in association with degeneration of the conjunctival epithelium. This late result may be prevented by the use of artificial tears which indicates the importance of early diagnosis.

The ocular test most widely used for diagnosis is the Schirmer test: filter paper strips placed under the eyelids at the inner canthus measure

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the quantity of tears secreted in 5 minutes in response to irritation. A normal young person usually wets 15 mm or more of the paper strip. Since hypolacrimation accompanies age, about one-third of presumably normal elderly persons may wet only 10 mm of the paper in 5 minutes. When wetting of 5 mm or less is employed as the cut-off point, about 15 percent of normal persons and patients with Sjögren's syndrome are misclassified.¹ This, then, is a crude test which is of limited value and may not be sensitive or specific enough for our usual clinical purposes. Since better tests are available, our attention should be directed to them. The relative merit of the various ocular diagnostic techniques has recently been reviewed.²

A simple and useful technique for the diagnosis of Sjögren's syndrome is measurement of tear lysozyme concentration by electrophoresis or by determining the diameter of lysis on agar plates impregnated with *M. lysodeikticus*. So tested, lysozyme concentration is found to be low in tears of patients with keratoconjunctivitis sicca and tends to vary with the severity of the disease. The test is highly reliable and yields excellent separation of normal subjects from patients with Sjögren's syndrome.

The characteristic signs of keratoconjunctivitis sicca are best evoked by ocular staining techniques. One of the most useful and widely employed materials for such staining is rose bengal, a fluorescein derivative. When a drop of rose bengal solution is instilled into the eye of a patient with Sjögren's syndrome, that portion of the eye which fills the palpebral aperture takes up the dye. In the fully developed disease, red triangles with their base toward the limbus are seen. The cornea, especially in its lower portion, is also stained (Figure 1). Such findings are pathognomonic of Sjögren's syndrome.

Salivary Gland Abnormalities

One of the major characteristics of Sjögren's syndrome is parotid enlargement. Approximately 25 to 50 percent of patients with Sjögren's syndrome present with enlargement of one or more parotid or submandibular glands. Salivary gland enlargement may occur in certain other diseases, such as hyperlipoproteinemia, malnutrition, cirrhosis of the liver, and diabetes mellitus. In such conditions, the glands tend to feel soft and puffy, and the mouth and eyes are not usually dry. The

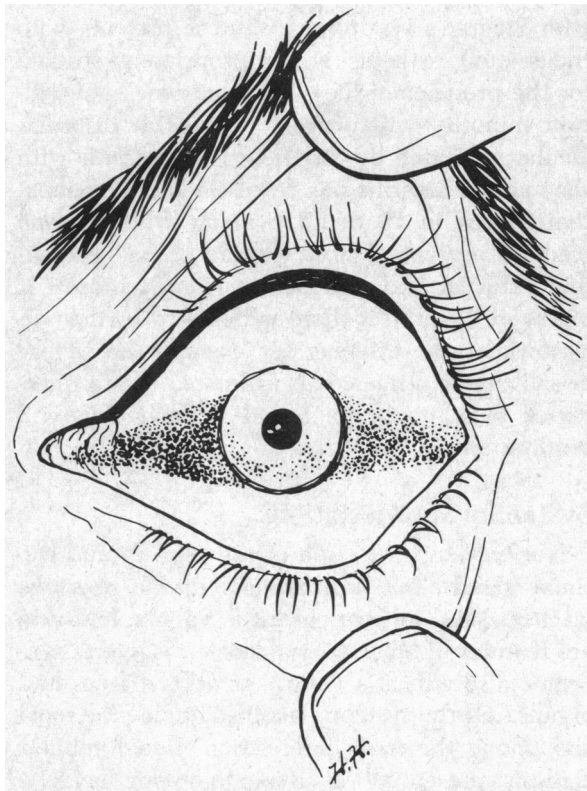


Figure 1.—Appearance of the eyes with rose bengal solution in keratoconjunctivitis sicca.

clinical setting in which the salivary enlargement occurs should help to suggest the diagnosis.

When the salivary glands become atrophic, saliva becomes deficient in quantity and is qualitatively altered, resulting in xerostomia. The mouth becomes exceedingly dry and the lips and oral mucous membranes become atrophic. The patient has difficulty in speaking, swallowing, and eating. Other effects of salivary gland atrophy are anosmia and rampant dental caries. Apparently saliva is necessary for healthy dentition. Its importance was demonstrated in a study in which the number of caries that developed in hamsters fed a cariogenic diet and simultaneously desalivated was ten times the number that occurred in those on the diet alone.³

A number of procedures have been employed to assess salivary gland function, including measurements of salivary flow, sialography, and salivary scintiscan. Sialography is a worthwhile adjunct to diagnosis, since the sialographic pattern is often abnormal even when the salivary glands are not clinically enlarged. It tends to correlate well with the degree of abnormality in

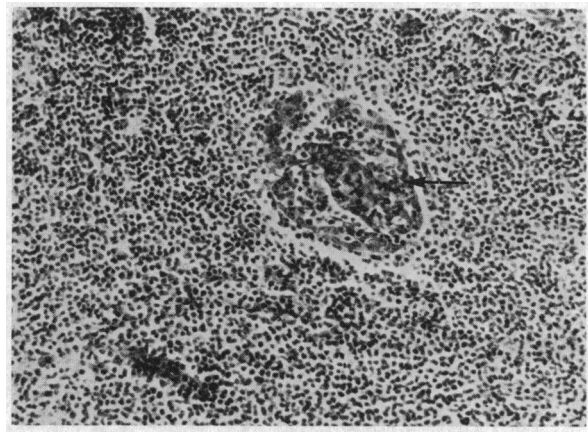


Figure 2.—Parotid biopsy specimen from patient with Sjögren's syndrome showing epimyoepithelial island (arrow) and intense lymphocytic infiltration.

the gland and with the severity of xerostomia. The procedure, however, may cause pain and swelling of the gland and there may be extravasation of the dye, which further disturbs glandular function. Allergic responses to contrast media have been recorded.

An extremely promising new technique for salivary gland evaluation is scanning with the radioactive element 99m technetium (^{99m}Tc). Normal salivary gland concentrates ^{99m}Tc, producing a bright image on the scintiscan; the diseased gland fails to concentrate this material appropriately.⁴ Sequential salivary scintigraphy yields curves of the uptake and excretion of ^{99m}Tc by salivary glands. In the normal gland there is rapid uptake, peaking at about a half-hour; radioactivity appears in the oral cavity in approximately 10 minutes. In patients with Sjögren's syndrome the curve usually fails to peak within an hour, and the oral cavity often shows no evidence of radioactivity throughout the study. This test is simple, free of side effects and non-invasive. It appears to be of special use in monitoring changes in salivary gland function induced by therapeutic maneuvers or that occur during the course of disease.

Confirmation of Sjögren's syndrome may be obtained by salivary gland biopsy. The pathological picture, apparently unique to this disease, has two basic features: massive lymphoid infiltration with atrophy of the acinar tissue, and ductal alterations characterized by intraductal cellular proliferation leading to narrowing of the lumen and eventually to the formation of compact cellu-

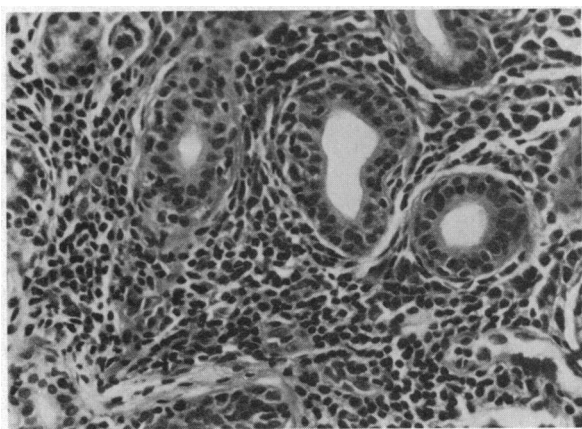


Figure 3.—Biopsy specimen of labial mucosa from a patient with Sjögren's syndrome showing intraductal cellular proliferation and lymphocytic infiltration.

lar structures which have been termed epimyoepithelial islands⁵ (Figure 2).

Since the minor salivary glands are also involved in the general polyglandular abnormality of Sjögren's syndrome, recent attention has focused on the labial glands as a convenient source of biopsy material. These are easily accessible; the biopsy procedure leaves no noticeable scar, and has few objectionable side effects. The histological abnormality of Sjögren's syndrome in the labial glands is similar to that in the major salivary glands, and permits diagnosis (Figure 3). This procedure, however, does not necessarily supplant parotid biopsy, which may still be required for patients who present with unilateral parotid swelling or other features that pose a diagnostic problem.

Associated Connective Tissue Diseases

One reason that Sjögren's syndrome has been of great interest to medicine is its frequent association with other disease. As Chart 1 shows, Sjögren's syndrome may be found in association with rheumatoid arthritis, scleroderma, lupus erythematosus, polymyositis, chronic hepatitis, Hashimoto's thyroiditis, pulmonary fibrosis, or lymphoproliferative neoplastic disorders. All have in common certain autoimmune characteristics; and in each, lymphocytic infiltration may involve certain major structures. Of the various disease states that may be found in association with Sjögren's syndrome, rheumatoid arthritis is most common. The criteria for its diagnosis are present in approximately 30 to 50 percent of patients

with Sjögren's syndrome,^{6,7} and if patients with rheumatoid arthritis are appropriately studied for the presence of Sjögren's syndrome, a significant minority will prove to have this disorder. Ocular screening by rose bengal in patients with rheumatoid arthritis has revealed keratoconjunctivitis sicca in 10 to 15 percent, while in one study 34 percent of those with advanced rheumatoid arthritis had this ocular complication.⁸ If one were to subject these patients to further diagnostic study, utilizing for example lip biopsy or salivary scintiscan, it is estimated that a quarter of them might be found to have Sjögren's syndrome.

Systemic Manifestations

Not only hypofunction of the salivary and lacrimal glands, but also dryness of the pharynx, trachea, nasal mucosa, bronchi, vagina, and skin are features of Sjögren's syndrome. Sjögren's syndrome also affects a variety of other tissues and organs. Of the systemic manifestations, the renal are among the most interesting. Renal tubular acidosis presenting as hyperchloremic acidosis may occur in approximately 20 percent of patients with Sjögren's syndrome. The defect in renal acidification is usually of Type I (classic, gradient, or distal). Such a defect is related to the inability of the distal nephron to overcome a steep hydrogen ion concentration gradient. Several cases of Sjögren's syndrome in association with physiological dysfunction of the proximal tubule have also been reported. In one of these cases, aminoaciduria, phosphaturia, uricosuria, and nephrogenic diabetes insipidus were present.² Renal tubular acidosis of a subclinical or incomplete form, lacking the overt feature of hyperchloremic acidosis, has also been noted in patients with Sjögren's syndrome and to be uncovered by an ammonium chloride loading test.⁹ Osteomalacia, nephrocalcinosis, and hypokalemia may all occur in association with the renal tubular acidosis of Sjögren's syndrome. Renal biopsy in patients with Sjögren's syndrome often reveals changes of chronic interstitial nephritis with lymphocytic infiltration and fibrosis of the interstitial areas, as well as periglomerular fibrosis and abnormalities of the tubules. The glomeruli are for the most part preserved. Electronmicroscopic studies have failed to show electron-dense deposits on the glomerular basement membrane.¹⁰ Interstitial nephritis may occur at any time during

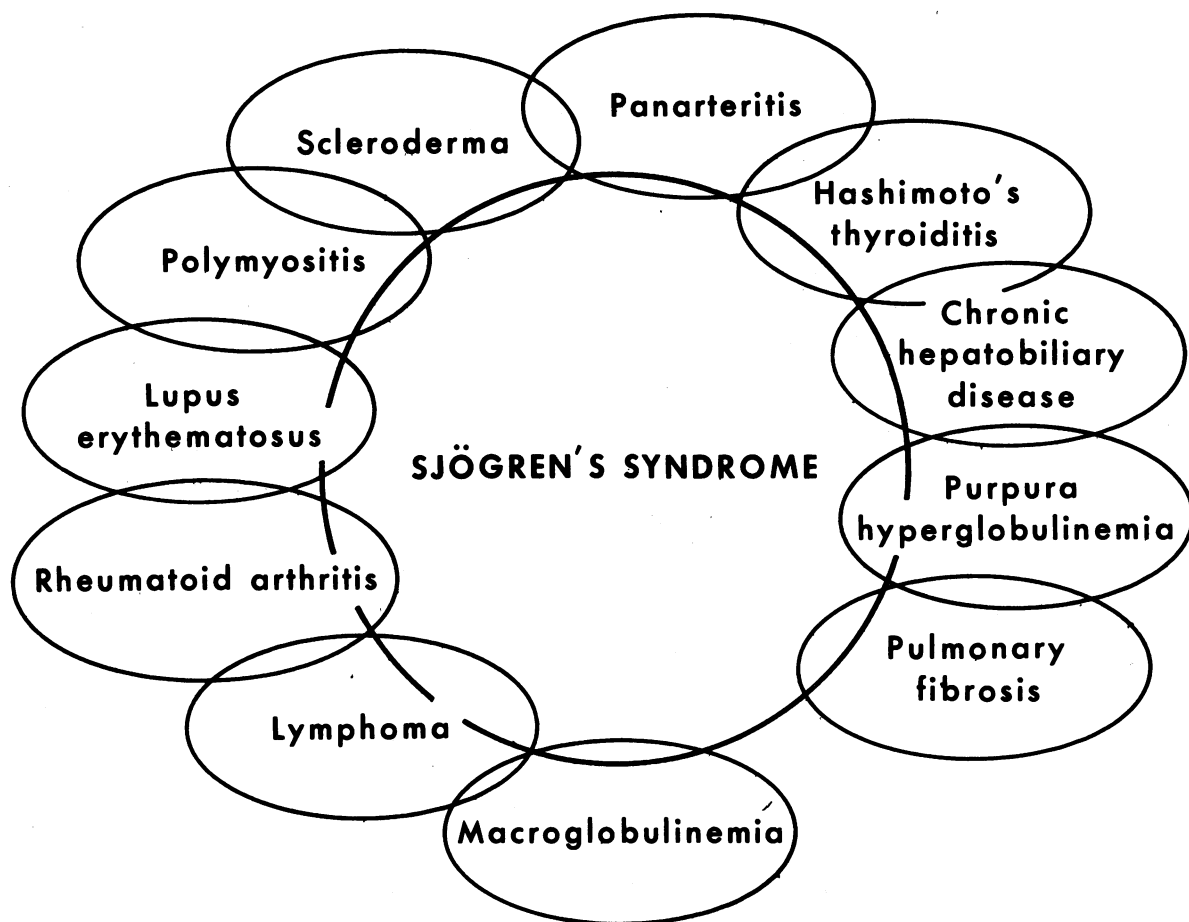


Chart 1.—The spectrum of disorders associated with Sjögren's syndrome. (From Shearn MA: Sjögren's Syndrome, Philadelphia, W. B. Saunders Co., 1971.)

the life history of the patient with Sjögren's syndrome, and in some it may progress to renal insufficiency and uremia.²

Although glomerulonephritis has been observed in patients with Sjögren's syndrome, it is rare, and usually associated with mixed cryoglobulinemia.¹¹ Why, in contrast to systemic lupus erythematosus, does Sjögren's syndrome often spare the glomerulus in spite of many clinical similarities between these two diseases? A possible explanation was provided by the demonstration of a striking absence of reactivity against deoxyribonucleic acid (DNA) in serum of patients with Sjögren's syndrome. Such reactivity is generally seen in patients with lupus erythematosus and immune complex disease.¹¹ Since antibodies to DNA may participate in the pathogenesis of soluble immune complex deposition, a possible explanation is thus offered for glomerular sparing in Sjögren's syndrome.

Lymphoproliferation

Another intriguing aspect of Sjögren's syndrome is the occurrence of lymphoproliferative neoplasms in an incidence far above that which could be explained by chance alone. To date some 40 or so patients have been reported to have Sjögren's syndrome and associated neoplasms, the majority being undifferentiated lymphomas. In Sjögren's syndrome there appears to be a spectrum of abnormalities ranging from lymphocytic infiltration in glandular structures, through intense lymphocytosis in organ structures, to frank lymphatic malignant neoplasia. Of 58 patients with Sjögren's syndrome in one study,¹² reticulum cell sarcoma developed in three and Waldenström's macroglobulinemia in a fourth. Other patients have been observed to have extrasalivary lymphoid abnormalities sufficiently pronounced to arouse clinical suspicion of lymphoma. In some of these cases lymph nodes

contain cells of primitive appearance which obscure the glandular landmarks.

Patients with lymphoid abnormalities are considerably more likely to show generalized lymph node enlargement, salivary gland swellings, splenomegaly, purpura, vasculitis, and neuropathy than those without such abnormalities. There is a lower incidence of rheumatoid arthritis in these patients than in patients with Sjögren's syndrome in whom lymphoproliferative diseases do not develop. Of interest is the fact that malignant lymphoma is being observed in a number of other clinical settings characterized by immunological aberrations and autoimmunity.¹³ Another possible parallel to Sjögren's syndrome is seen in mice that survive a graft-versus-host reaction, then succumb to malignant lymphoma. In addition, lymphoma develops with relative frequency in the New Zealand Black (NZB) mouse, which incurs a disease in many ways similar to Sjögren's syndrome.

Immunological Findings

One of the most characteristic features of Sjögren's syndrome is the remarkable immunological reactivity detected in serum. In the majority of patients with Sjögren's syndrome, the serum contains antigammaglobulin antibodies, antinuclear antibodies and gamma globulin in heightened concentrations. A gamut of other serological abnormalities, including antibodies against salivary duct, lacrimal gland, smooth muscle, mitochondria, and thyroid gland have all been noted. Rheumatoid factor has been detected in over 90 percent of cases, irrespective of the presence or absence of rheumatoid arthritis.⁶ About 50 percent of patients have antibodies directed against salivary duct cells,¹⁴ and the LE preparation is positive in some 15 to 20 percent of patients with Sjögren's syndrome. Serological abnormalities tend to occur in families of patients with Sjögren's syndrome and are seen in family members without overt evidence of disease.² In spite of the tendency to increased humoral antibody concentrations, cell-mediated immunity has been shown to be impaired in Sjögren's syndrome. Peripheral blood lymphocytes are functionally abnormal in their response to mitogenic agents. Patients with Sjögren's syndrome also have a decreased capacity to develop delayed hypersensitivity to a specific contact allergen.¹⁵ Thus it seems that there is a discordance of thymus (T) cell and

bone marrow (B) cell function. Since cell-mediated immunity appears to play a vital role in immunological surveillance against clones of cells with oncogenic potential, depression of this function would seem to have special meaning in a disease with increased incidence of malignant neoplasia.

Other laboratory abnormalities include elevated sedimentation rate in approximately two-thirds of the patients, anemia in one-third, and leukopenia and eosinophilia in about one-fourth.

NZB Mouse

The NZB mouse, a highly inbred New Zealand strain originally developed for cancer research, spontaneously develops autoimmune hemolytic anemia with a high incidence of positive direct Coombs tests and, less commonly, antinuclear antibodies. In the hybrid produced by crossing the NZB mouse with another inbred strain, the New Zealand White (NZW), a disease remarkably similar to systemic lupus erythematosus developed, including alopecia, skin lesions, splenomegaly, hepatomegaly, autoimmune hemolytic anemia, and immune complex nephritis. Antinuclear antibodies, positive LE preparations, and a high incidence of double-stranded DNA were found in the blood. Of special interest was observation of the characteristic histopathological features of Sjögren's syndrome in the salivary gland tissue of those animals that were studied after four months of life.¹⁶ As the mice aged, salivary gland abnormalities increased and typical epimyoepithelial islands were seen. The cornea and conjunctiva showed changes similar in many ways to the ocular features of Sjögren's syndrome in man. These mice harbored the Gross leukemia virus; and cell-free filtrates from them, injected intraperitoneally into young adult Swiss-Webster mice, produced lymphoid cell hyperplasia, glomerulonephritis, and hypergammaglobulinemia in these animals.¹⁷ Also of note was the development of lymphomas in approximately 10 percent of the NZB-NZW hybrids.

The possible parallels of the mouse disease to Sjögren's syndrome as it occurs in man have been most intriguing. In the mouse the interaction of genetic, immunological, and viral factors appears to account in large part for the disease process. If we were to extrapolate to man, would it be possible that in a susceptible, genetically predis-

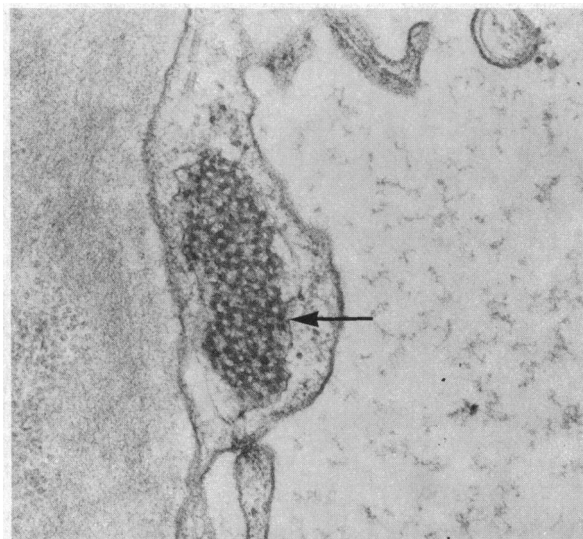


Figure 4.—Electron micrograph of renal biopsy specimen from a patient with Sjögren's syndrome showing microtubular structure (arrow) within a cytoplasm of endothelial cell. (From Shearn MA: *Sjögren's Syndrome*, Philadelphia, W. B. Saunders Co., 1971.)

posed individual with altered immunologic balance, a slowly acting agent such as a latent virus might produce the disease? Thus far, evidence has not been forthcoming that human Sjögren's syndrome is a viral disease. However, microtubular structures similar to those observed in systemic lupus erythematosus have now been seen in cells from several organs (Figure 4) as well as in circulating lymphocytes of patients with Sjögren's syndrome. Although much controversy surrounds the nature of these structures many investigators believe they are not actually viruses but are in some manner virus-related—

perhaps the trace or evidence that a virus has been present.

The further elucidation of the responsible host and environmental factors that participate in the etiology of Sjögren's syndrome should prove important to our understanding not only of other connective tissue diseases, but also of the relation of autoimmunity to malignant neoplasia.

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HYPOPHYSECTOMY FROM ABOVE—NOT FOR DIABETICS

Doing any type of hypophysectomy from above in diabetics is bad business. About ten years ago at Memorial Hospital this procedure was done for two kinds of cases—diabetic retinopathy and metastatic breast cancer. It turned out that in the breast cancers there were never any postoperative convulsions. But in 90 percent of the diabetics there were convulsions over periods as long as five years. The vasculature is so poor in these people that by reflecting the frontal lobes and pushing them around, you create damage that leads to convulsions. This fact led many people to give up hypophysectomy from above in late-stage diabetics.

—PANEL DISCUSSION ON MANAGEMENT OF DIABETIC RETINOPATHY
Extracted from *Audio-Digest Ophthalmology*, Vol. 9, No. 13, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057